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Attenuating Collagen Deposition by Synoviocytes from Osteoarthritic Patients with Synovial Fibrosis

Fibrosis is the deposition of stiff extracellular matrix mostly composed of type-I collagen (COL1), which can impair function of diseased musculoskeletal components. COL1 is synthesized by myofibroblasts and mostly driven by the receptor-mediated transforming growth factor (TGF)β1-ALK5-Smad2/3 cascade. Stimulation of naïve fibroblasts with TGFβ1 induces proliferation, smooth muscle actin (SMA)+ myofibroblast differentiation, and COL1 synthesis. COL1 undergoes modifications to its triple helix, such as the conversion of lysine to hydroxylysine by *Plod2*-encoded lysyl hydroxylase (LH) 2b to facilitate cross-links that effectively strengthen COL1 fibrils. Synovial fibrosis (SFb) is a hallmark of osteoarthritis (OA) characterized by aberrant COL1 deposition in the subintima of the synovium encapsulating the joint. Current interventions for fibrous arthropathy, including manipulation under anesthesia and arthroscopic lysis of adhesions, are expensive and not guaranteed to relief stiffness. We have performed histological analyses of banked synovium from OA patients undergoing total knee arthroplasty (TKA) and published evidence that SFb presents heterogeneously between patients regardless of disease stage and that severe SFb associates with race and high deficits in range of motion (ROM). To expand on the differential molecular profile of OA patients grouped by low and high SFb, we detected LH2b on a specimen subgroup from the published cohort that resulted in LH2b levels corresponding to severity of SFb. This suggests that high SFb patients may also present stronger COL1 deposits.

Minoxidil (MXD) is an FDA-approved treatment for hypertension and alopecia. Recently, studies on the disruption of the collagenous network engineered by cancer-associated fibroblasts to facilitate metastasis and studies on clubfoot fibroblasts have shown that MXD interferes with the transcription of LH2b, consequently weakening COL1 by limiting over-hydroxylation of telopeptides and associated pyridinoline (Pyd) cross-links in newly synthesized collagen. We hypothesize that MXD will compromise the amount and integrity of collagen deposits generated by synovial fibroblasts derived from OA patients presenting with high SFb.

We propose to apply MXD to cultured primary fibroblasts from OA patients classified with high SFb and naïve fibroblasts challenged with TGFβ1. Isolated protein from the same homogenates will be analyzed by ELISA of Pyd cross-links as well as for hydroxyproline content. Comparisons will be tested by ANOVA. We expect MXD treatment to not interfere with TGFβ1 signaling or COL1 production but decrease transcription of LH2b and resultantly lower Pyd content. Altogether, our goal is to test anti-fibrotics such as MXD to attenuate SFb and improve conventional strategies for OA knee stiffness.